REMARKS

Claims 21-38, 40-46, 48-54, 56, 57 and 63 are currently pending in this application. No new matter has been added.

Obviousness rejections over Muller and Andersson are Overcome

Claims 21-38, 40-46, 48-54, 56, 57 and 63 remain rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,858,410 ("Muller") in view of U.S. Patent No. 5,739,152 ("Andersson"). Applicants disagree.

Specifically, as the Examiner indicated in the Office Action of January 23, 2008, Muller teaches nanosuspensions comprising 0.001-30% lecithin and the compounds polyvinyl alcohol, poloxamer, glucose, mannose trehalose, and sorbitol at 0.1-2% and at 0.1-30%; as well as, disclosing parental, intramuscular and subcutaneous administration, active ingredients such as cyclosporine and autoclaving. (*See*, Office Action at page 3). The Examiner further alleged in the previous Office Action that Andersson teaches autoclaving a dispersion of active agent under nitrogen to achieve a stable compositions. (*See*, Office Action at page 3).

First, Applicants submit that the teachings of Muller and Andersson do not teach or suggest each of the limitations of the claims and that the Examiner has not explained why despite these differences the subject matter of the claims is obvious over the teachings of Muller and Andersson. Second, Applicants assert that claims 21-38, 40-46, 56, 57 and 63 are based upon unexpected results so that one of ordinary skill in the art would not have a reasonable expectation of success in the methods of the instant claims in light of the teachings of Muller and Andersson. Third, Applicants submit that the teachings of Muller and Andersson teach away from the composition of claims 21-38, 40-46, 56, 57 and 63.

Muller and Andersson do not teach or suggest all claim limitations

Applicants submit that Muller and Andersson do not teach or suggest the limitations of claims 21-38, 40-46, 48-54, 56, 57 and 63 in light of the general knowledge of one of ordinary skill in the art.

Prior art is not limited just to the references being applied, but includes the understanding of one of ordinary skill in the art. The prior art reference (or references when combined) need

not teach or suggest all the claim limitations, however, Office personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art.[1]

Again, Applicants submit that Muller does not teach an autoclavable composition of an aqueous injectable, terminally steam sterilized suspension in a vial sealed under nitrogen atmosphere, said suspension consisting essentially of particles of a water insoluble or poorly soluble biologically active substance with a volume weighted mean particle size of up to 3 μm, with not more than 3000 particles of a size of 10 μm or greater and not more than 300 particles of a size of 25 μm or greater, said particles surface stabilized with one or more phospholipid surface modifiers, and a pharmaceutically acceptable amount of a water soluble polyhydroxy thermoprotecting agent selected from the group consisting of trehalose, lactose, dextrose, sorbitol, dextran, mannitol and mixtures thereof, wherein the ratio of said active substance to said phospholipid surface modifier is from about 3:1 to about 5:1 and the amount of said phospholipid surface modifier is in the range from about 0.2% w/w to about 5.0% w/w, wherein said composition is devoid of surfactants that require during terminal steam sterilization elevation of their cloud point temperature by addition of a cloud point modifier, said composition being devoid of surfactant additives which coagulate on steam sterilization, and further wherein the volume weighted mean particle size of said particles is not increased more than two-fold during and after terminal steam sterilization. Applicants further submit that Muller does not teach an autoclavable composition of an injectable, non-flocculating, aqueous, terminally steam sterilized suspension under nitrogen in a sealed vial, said suspension consisting essentially of particles of a water insoluble or poorly soluble drug substance with a volume weighted mean particle size of up to 3 μm, said particles surface stabilized with one or more phospholipid surface modifiers, and a pharmaceutically acceptable amount of a water soluble polyhydroxy thermoprotecting agent, wherein (i) the ratio of said drug substance to said surface modifier is about 3:1 to about 5:1, (ii) the amount of said surface modifier is in the range from about 0.2% w/w to about 5.0% w/w, and (iii) said volume weighted mean particle size is not increased more than two-fold during and after terminal steam sterilization, and wherein said composition is devoid of surfactants that require during terminal steam sterilization elevation of their cloud

[1] MPEP § 2141

point temperature by addition of a cloud point modifier and is devoid of surfactant additives which coagulate on steam sterilization, and the ratio of the amount of the active substance and the thermoprotecting agent is selected to provide particle size stability during and after terminal steam sterilization.

Specifically, the claims 21, 22, and 38, from which the remaining rejected claims properly depend, require that the composition be *devoid* of surfactants that require during terminal steam sterilization elevation of their cloud point temperature by addition of a cloud point modifier, said composition being *devoid* of surfactant additives which coagulate on steam sterilization (*emphasis added*). The specification teaches that the present invention differs in that previous formulations include surfactants that coagulate upon steam sterilization, *i.e.* polyvinylpyrrolidine ("PVP"), polyethylene glycols and polyvinyl alcohol. (*See*, Specification at page 2, line 29 through page 3, line 1 and at page 4, lines 2-4). Further, the specification indicates that the formulations are absent of agents that have a high concentration of hydrogen or hydroxyl ions. (*See*, Specification at page 4, lines 1-2). These excluded compounds have a natural tendency to coagulate at high temperatures. (*See*, Specification at page 4, lines 4-5).

In contrast, Muller teaches adding substances such as PVP, which is explicitly excluded from the claimed formulations as well as Pluronic F68, a difunctional block copolymer surfactant terminating in primary hydroxyl groups, which as indicated above, comprises the hydroxyl ions that are not to be included in the claimed formulation. (*See*, http://www2.basf.us/performancechemical/pdfs/Pluronic_F68.pdf enclosed herewith as Exhibit A). Additionally, Muller, at column 7, lines 25-27, includes ethoxylated stabilizers such as Tween 80 (*i.e.* polysorbate 80) among the surfactants included in the formulation, which also is compound which has a high concentration of hydroxyl ions, and thus is excluded from the claimed invention. Examples 1-4, 6-12, and 14-16 of Muller teach using Tween or Pluronic F68 in the formulation. Whereas the instant invention teaches the use of LIPOID 80 as the phospholipid and when a surface modifier, such as Pluronic F68 is added, the mean particle size of the composition, upon steam sterilization, increases tremendously, *i.e.* from 0.86 μm to 4.22 μm. (*See*, specification at Table II).

Also, as previously submitted, Muller only teaches one composition devoid of surfactant, but this composition does not meet the limitations of the claims recited above. The composition

of Muller that does not initially contain a surfactant had to have sodium carboxymethylcellulose added during the homogenization process to increase the viscosity of the composition as sedimentation was occurring. (*See*, Muller at column 8, lines 27-33; and at column 17, lines 1-15). As such, the composition is no longer devoid of surfactant additives as required by the instant claims.

Andersson does not cure the deficiencies of Muller. As alleged by the Examiner, Andersson teaches sterilization under nitrogen, but does not teach any compositions like the ones encompassed by claims 21-38, 40-46, 48-54, 56, 57 and 63. Thus, Applicants submit that the teachings of Muller and Andersson do not teach or suggest all of the limitations of claims 21-38, 40-46, 48-54, 56, 57 and 63.

Unexpected Results.

Applicants re-assert that a person having ordinary skill in the art reviewing the cited references would not have arrived at claims 21-38, 40-46, 56, 57 and 63 because of the composition of the claims are based on unexpected results, which are confirmed by the Declaration under 37 CFR § 1.132 of Awadhesh K. Mishra submitted herewith ("the Mishra Declaration"), which is evidence that the composition of these claims is non-obvious over Muller and Andersson.

As discussed above, the claimed compositions do not contain any surfactant that would require cloud point modifying molecules for protection against coagulation, flocculation, crystal growth, or particle size growth during the terminal steam sterilization process. Formulations without surfactants are generally known by a person of ordinary skill in the art to have a tendency to coagulate upon steam sterilization.

The specification teaches, unexpectedly from the standpoint of one of ordinary skill in the art at the time the invention was made, that the claimed compositions of submicron- to micron-sized particulate suspension of water insoluble or poorly water-soluble pharmaceutical agents with only the addition of a phospholipid and thermoprotecting agent, can be autoclaved without any marked increase in mean particle size. (*See*, Specification at page 2, paragraph 3 and the Mishra Declaration at point 4). The compositions also withstood stresses that are known by a person of ordinary skill in the art to promote particle size growth, flocculation, or agglomeration.

(*See*, Specification at page 2, paragraph 4 and the Mishra Declaration at point 5). Further, the claimed compositions were successfully lyophilized before or after steam sterilization and the same preparations could be reconstituted by the addition of water to make an aqueous suspension having qualities similar to the original suspension. (*See*, Specification at page 2, paragraph 5 and the Mishra Declaration at point 6).

As evidenced by the Mishra Declaration, these results are unexpected in light of the teachings of Muller and Andersson, as Muller does not teach or suggest a composition with only a phospholipid without the addition of a surfactant. Further, as discussed above, Muller teaches a surfactant free formulation, however, it suffered from sedimentation issues during processing. Moreover, Andersson, as articulated above, merely teaches autoclaving emulsions capable of being autoclaved under nitrogen. Thus, Applicants submit that the methods of claims 21-38, 40-46, 56, 57 and 63 are based on unexpected properties and thus are non-obvious over Muller and Andersson.

Muller and Andersson teach away from the subject matter of the claimed invention

Applicants re-submit that one of ordinary art would be led away from the invention of claims 21-38, 40-46, 56, 57 and 63 based on the teachings of Muller and Andersson. Specifically, the Examiner has not addressed the argument in the final Office Action. Andersson merely teaches oil-in-water emulsions comprising a short active compound, a lipid phase, and emulsifier and water capable of being autoclaved under nitrogen. (*See*, Andersson at column 1, lines 44-51 and at column 6, line 9). The stable compositions taught by Muller require the addition of a surfactant as well as a surface modifier, *i.e.* a phospholipid. (*See*, Muller at column 8, lines 19-33). Muller teaches that sterilization of nanosuspensions stabilized with varying surfactant concentrations resulted in the lowest particle growth at a Tween 80 concentration of 0.03% to 0.1%. (*See*, Muller at column 8, lines 19-24). Further, Muller discloses that the addition of the lowest possible amount of surfactant is desirable from a toxicological aspect, however, the surfactant-free composition in example 13, had to have sodium carboxymethylcellulose added during the homogenization process to increase the viscosity of the composition. (*See*, Muller at column 8, lines 27-33). Moreover, as explained above, the composition of Example 13 does not meet the limitations of claims 21-38, 40-46, 48-54, 56, 57

and 63. Thus, Muller teaches that the addition of a surfactant is necessary to form the nanosuspensions described in Muller.

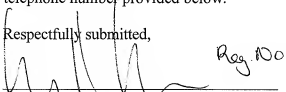
In contrast, claims 21, 22 and 38, from which claims 23-37, 40-46, 48-54, 56, 57 and 63 depend, require that the composition be *devoid* of surfactant that require during terminal steam sterilization elevation of their cloud point temperature by addition of a cloud point modifier. Similarly, the instant claims require that the composition be *devoid* of surfactant additives which coagulate upon steam sterilization. As articulated above, Muller teaches that surfactants are necessary, despite potentially toxic effects, in order to stabilize compositions similar to those claimed by the instant application. Thus, the teachings of Muller would lead one of ordinary skill in the art away from the invention of claims 21-38, 40-46, 56, 57 and 63.

As explained above, Applicants submit that the Examiner's obviousness rejection is improper as Muller and Andersson do not teach or suggest all the limitations of the claimed invention, Muller and Andersson teach away from the claimed invention, and the compositions of claims 21-38, 40-46, 56, 57 display unexpected properties. Thus, Applicants submit that claims 21-38, 40-46, 56, 57 and 63 are not obvious over Muller and Andersson, and respectfully requests that this rejection be withdrawn.

Conclusion

Applicants submit that this paper is fully responsive and that the application is in condition for allowance. Should any questions arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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